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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/631,874	07/31/2003	Indranil Nandi	G-33302P1	1795

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EXAMINER	
HENRY, MICHAEL C	
ART UNIT	PAPER NUMBER
1623	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/631,874	NANDI ET AL.	
	Examiner	Art Unit	
	MICHAEL C. HENRY	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/02/07 has been entered.

The following office action is a responsive to the Amendment filed, 10/02/07.

The amendment filed 10/02/07 affects the application, 10/631,874 as follows:

Claim 20 has been amended. Applicant's amendment has overcome the 112 2nd rejection.

The responsive to applicants' amendments is contained herein below.

Claims 1-20 are pending in the application

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Domet et al. (US 4,929,605) in combination with Maekawa et al. (US 4,176,175).

In claim 1, applicant claims "A pharmaceutical composition consisting essentially of fexofenadine or a pharmaceutical acceptable acid addition salt thereof, about 10 wt. % to about 70 wt. % of lactose, and about 1 wt. % to about 40 wt. % of a low-substituted hydroxypropyl

cellulose, wherein the weight percents are based on the total weight of the pharmaceutical composition." Dependent claims 2-13 are drawn to specific wt. % and mg of the components of said composition. Claims 14-17 are drawn to low-substituted hydroxypropyl cellulose of specific average particle sizes and wt. %.

Domet et al. disclose a pharmaceutical composition in solid unit dosage form containing a therapeutically effective amount of a piperidinoalkanol compound, such as fexofenadine and terfenadine, or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable nonionic or cationic surfactant, and a pharmaceutically acceptable carbonate salt. Furthermore, Domet et al. disclose that said piperidinoalkanol derivatives (compounds) which are antihistamines, antiallergic agents and bronchodilators, are in general, only minimally soluble in water and therefore the therapeutically inactive ingredients in a pharmaceutical composition containing one or more of these compounds are very important in providing for their efficient and immediate absorption and bioavailability after oral administration (see col. 1, lines 11-33). It should be noted that piperidinoalkanol compounds fexofenadine and terfenadine, which are useful as antihistamines, antiallergic agents and bronchodilators are quite similar in structure, differing only by a substituent (i.e. methyl group as opposed to a carboxyl group).

The difference between applicant's claimed composition and the composition disclosed by Domet et al. is that applicant's composition contains lactose and low-substituted hydroxypropyl cellulose.

Mackawa et al. disclose that solid drugs preparation (dosage form) such as tablets, granules and pill that are coated with sugars containing low-substituted hydroxypropyl cellulose improves the disintegration time (see abstract). Furthermore, Mackawa et al. disclose that sugars

in general such as sucrose (which like lactose is a disaccharide) can be used (see col. 2, lines 23-37).

It would have been obvious to one having ordinary skill in the art, at the time the claimed invention was made, in view of Domet et al. and Maekawa et al., to have prepared a pharmaceutical composition comprising fexofenadine, low-substituted hydroxypropyl cellulose and lactose and to be used as an antihistamine composition, since Domet et al. disclose that there is a need for the immediate absorption and bioavailability of piperidinoalkanol compounds (derivatives) including fexofenadine and terfenadine (after oral administration) and Maekawa et al. disclose that specific components such low-substituted hydroxypropyl cellulose and sugars such as lactose and improves the rapid disintegration and favorable release (i.e.,bioavailability) of drugs.

One having ordinary skill in the art would have been motivated in view of Domet et al. and Maekawa et al., to have prepared a pharmaceutical composition comprising fexofenadine, lactose and low-substituted hydroxypropyl cellulose to be used as an antihistamine composition, since Domet et al. disclose that there is a need for the immediate absorption and bioavailability of piperidinoalkanol compounds (derivatives) including fexofenadine and terfenadine (after oral administration) and Maekawa et al. disclose that specific components such low-substituted hydroxypropyl cellulose and sugars such as lactose and improves the rapid disintegration and favorable release (i.e.,bioavailability) of drugs. It should be noted that the use of specific quantities (e.g., mg), wt. % and type of low-substituted hydroxypropyl cellulose of said composition depends on the need, such as the individual to which this composition is administered.

Claims 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Domet et al. (US 4,929,605) in combination with Obara et al. (US 6,380,381 B1).

In claim 18, applicant claims "A method of preparing a pharmaceutical composition consisting essentially of fexofenadine or a pharmaceutical acceptable acid addition salt thereof, about 10 wt. % to about 70 wt. % of lactose, and about 1 wt. % to about 40 wt. % of a low-substituted hydroxypropyl cellulose, wherein the weight percents are based on the total weight of the pharmaceutical composition, said method comprising:

(a) mixing fexofenadine, lactose, and low-substituted hydroxypropyl cellulose to form a premix;

(b) adding a solvent to the premix formed in Step (a) to form a wet granulation; and

(c) drying the wet granulation to form dried granules;

(d) mixing at least one excipient with the dried granules to form a pharmaceutical composition." Claim 19 is drawn to a method of preparing a pharmaceutical composition consisting essentially of fexofenadine or a pharmaceutical acceptable acid addition salt thereof, about 10 wt. % to about 70 wt. % of lactose, and about 1 wt. % to about 40 wt. % of a low-substituted hydroxypropyl cellulose, wherein the weight percents are based on the total weight of the pharmaceutical composition, said method comprising: (a) mixing fexofenadine, lactose, and low-substituted hydroxypropyl cellulose to form a premix;…….. Claim 20 is drawn to the method according to claim 19 further comprising the step of milling the dried using a conical screen.

Domet et al. disclose a method of preparing a pharmaceutical composition in solid unit dosage form containing a therapeutically effective amount of a piperidinoalkanol compound, such as fexofenadine and terfenadine comprising mixing said piperidinoalkanol compound with a pharmaceutically acceptable nonionic or cationic surfactant and a pharmaceutically acceptable carbonate salt and forming granules which are dried and milled to uniform size (see col. 4, lines 50-64). Furthermore, Domet et al. disclose that said piperidinoalkanol derivatives (compounds) which are antihistamines, antiallergic agents and bronchodilators, are in general, only minimally soluble in water and therefore the therapeutically inactive ingredients in a pharmaceutical composition containing one or more of these compounds are very important in providing for their efficient and immediate absorption and bioavailability after oral administration (see col. 1, lines 11-33). It should be noted that the piperidinoalkanol compounds fexofenadine and terfenadine, are useful as antihistamines, antiallergic agents and bronchodilators.

The difference between applicant's method and the method disclosed by Domet et al. is that applicant's uses low-substituted hydroxypropyl cellulose in their composition.

Obara et al. disclose that low-substituted hydroxypropyl cellulose exhibits good granulation characteristics and tablet properties (i.e. improving bioavailability) (see abstract). Furthermore, Obara et al. exemplify the preparation of a good granulation composition comprising the low-substituted hydroxypropyl cellulose and lactose (see col. 4, line 45-56). Also, Obara et al. disclose that for the low-substituted hydroxypropyl cellulose of the present invention, that tablet may be prepared that contain, for example, active ingredients, lubricants (e.g., magnesium stearate), excipients (e.g., corn starch and lactose), and other disintegrators and binders (see col. 3, line 64 to col. 4, line 4). Obara et al disclose a low-substituted

hydroxypropyl cellulose having a hydroxypropoxyl content in the range of 5.0 to 16.0% by weight and an apparent average degree of polymerization in the range of 350 to 700 (see abstract). In addition, Obara et al. disclose that low-substituted hydroxypropyl cellulose, its degree of substitution provides good granulation such that it improves the disintegration properties of tablets (i.e. improving bioavailability) (see col. 1, lines 21-59).

It would have been obvious to one having ordinary skill in the art, at the time the claimed invention was made, in view of Domet et al. and Obara et al., to have used the method of Domet et al. to prepare a pharmaceutical composition comprising fexofenadine, low-substituted hydroxypropyl cellulose and lactose to be used as an antihistamine composition, since Domet et al. disclose that there is a need for the immediate absorption and bioavailability of piperidinoalkanol compounds (derivatives) including fexofenadine (after oral administration) and Obara et al. disclose that a good granulation such as low-substituted hydroxypropyl cellulose and lactose improves the bioavailability (i.e. rapid disintegration and favorable release) of drugs.

One having ordinary skill in the art would have been motivated in view of Domet et al. and Obara et al., to have used the method of Domet et al. to prepare a pharmaceutical composition comprising fexofenadine, low-substituted hydroxypropyl cellulose and lactose to be used as an antihistamine composition, since Domet et al. disclose that there is a need for the immediate absorption and bioavailability of piperidinoalkanol compounds (derivatives) including fexofenadine (after oral administration) and Obara et al. disclose that a good granulation such as low-substituted hydroxypropyl cellulose and lactose improves the bioavailability (i.e. rapid disintegration and favorable release) of drugs. It should be noted that the use of specific quantities (e.g., mg), wt. % and type of low-substituted hydroxypropyl cellulose of said

composition depends on the need, such as the individual to which this composition is administered. In addition, the use of specific mills such as a low shear mill is commonly used in the art in the preparation of such oral tablet formulations, and is well with the purview of a skill artisan does not appear to alter the said composition formed.

Response to Arguments

Applicant's arguments with respect to claim 1-20 have been considered but are not found convincing.

The applicant argues that fexofenadine is structurally different to terfenadine. However, fexofenadine is functionally equivalent to terfenadine in terms of both being antihistamines or anti-allergy agents (see also Domet et al., col. 42-44). In addition, the structural difference between terfenadine and fexofenadine is not considered to be significant, especially since that both have the same structural core. But more importantly, fexofenadine is functionally equivalent to terfenadine in terms of both being antihistamines or anti-allergy agents (see also Domet et al., col. 42-44).

The applicant argues that Domet makes no mention of fexofenadine and states that terfenadine is the preferred active ingredient. However, Domet et al. disclose a piperidinoalkanol compound (e.g. compounds of the formula (3) (see col. 2, lines 36-63), which includes fexofenadine and terfenadine, are antihistamines, antiallergic agents and bronchodilators (i.e., they are functionally equivalent) (see also Domet et al., col. 42-44). Thus, it is obvious to one of ordinary skill in the art, based on Domet et al.'s teaching, to the substitute the functionally equivalent fexofenadine for terfenadine.

The applicant argues that as the Applicants have stressed before, terfenadine and fexofenadine have significant structural differences in that fexofenadine terminates in a carboxylic acid group while tertfenadine terminates with a simple methyl group. This is not, as the Examiner suggests, a minor difference in substituent groups. This is a complete change in the functional group which terminates the molecule. One of ordinary skill would expect such a change to significantly affect the reactivity of the molecule and thus its likely pharmaceutical effectiveness. He or she would no more expect terfenadine and fexofenadine to be interchangeable with one another than he or she would expect acetic acid and ethane gas to be interchangeable with one another. However, the structural difference between terfenadine and fexofenadine is not considered to be significant, especially since that both have the same structural core. But more importantly, fexofenadine is functionally equivalent to terfenadine in terms of both being antihistamines or anti-allergy agents (see also Domet et al., col. 42-44). Consequently, one of ordinary skill would expect the reactivity of both molecules and thus their likely pharmaceutical effectiveness in terms of being an antihistamines or anti-allergy agents to be similar.

The applicant argues that the Maekawa patent, however, says absolutely nothing about lactose. While Maekawa repeatedly speaks of using "sugar", the only sugar specifically referred to in Maekawa is sucrose, not lactose. Consequently, then, one of skill following the teaching of Mackawa would have been lead to use sucrose rather than lactose in any pharmaceutical composition since this was clearly Mackawa's preferred (and apparently only) embodiment. On the contrary however, Maekawa et al. disclose that sugars in general such as sucrose (which like lactose is a disaccharide) can be used (see col. 2, lines 23-37). Consequently, one of ordinary

skill in the art following the teaching of Mackawa would have been motivated to any sugar taught by Mackawa, especially a disaccharide sugar such as lactose that is similar and common like sucrose base on factors such as availability, cost and/or need.

The applicant argues that Domet alone certainly cannot be said to suggest the step of "mixing fexofenadine, lactose, and low-substituted hydroxypropyl cellulose to form a premix." However, the rejection set forth above was made by combining Domet and Macekawa or Domet and Obara. And, the motivation to combination is clearly set forth in the above rejections (see rejection above).

The applicant argues that as for the Obara patent, this reference merely discloses "low-substituted hydroxypropyl cellulose having good granulation characteristics and tablet properties." See Obara, Col. 1, lines 6 - 8. Obara says nothing about using this low-substituted hydroxypropyl cellulose with fexofenadine or any other form of piperidinoalkanol derivative. In fact, Obara does not specify any form of active pharmaceutical ingredient which is said to be suitable for use with the low- substituted hydroxypropyl cellulose described therein. Accordingly, Obara also fails to suggest the step of "mixing fexofenadine, lactose, and low-substituted hydroxypropyl cellulose to form a premix." However, Domet et al. disclose that said piperidinoalkanol derivatives (compounds) which are antihistamines, antiallergic agents and bronchodilators, are in general, only minimally soluble in water and therefore the therapeutically inactive ingredients in a pharmaceutical composition containing one or more of these compounds are very important in providing for their efficient and immediate absorption and bioavailability after oral administration (see col. 1, lines 11-33). It should be noted that the piperidinoalkanol compounds fexofenadine and terfenadine, are useful as antihistamines, antiallergic agents and

bronchodilators. Consequently, One having ordinary skill in the art would have been motivated in view of Domet et al. and Obara et al., to have used the method of Domet et al. to prepare a pharmaceutical composition comprising fexofenadine, low-substituted hydroxypropyl cellulose and lactose to be used as an antihistamine composition, since Domet et al. disclose that there is a need for the immediate absorption and bioavailability of piperidinoalkanol compounds (derivatives) including fexofenadine (after oral administration) and Obara et al. disclose that a good granulation such as low-substituted hydroxypropyl cellulose and lactose improves the bioavailability (i.e. rapid disintegration and favorable release) of drugs (also see above rejection).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Henry whose telephone number is 571-272-0652. The examiner can normally be reached on 8.30am-5pm; Mon-Fri. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael C. Henry

April 13, 2008.

/Shaojia Anna Jiang, Ph.D./

Supervisory Patent Examiner, Art Unit 1623